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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 213/40, A61K 31/44
C07D 307/52, A61K 31/34

A1

(11) International Publication Number: WO 94/03429

(43) International Publication Date: 17 February 1994 (17.02.94)

(21) International Application Number: PCT/GB93/01601

(22) International Filing Date: 28 July 1993 (28.07.93)

(30) Priority data:
9216289.0 31 July 1992 (31.07.92) GB

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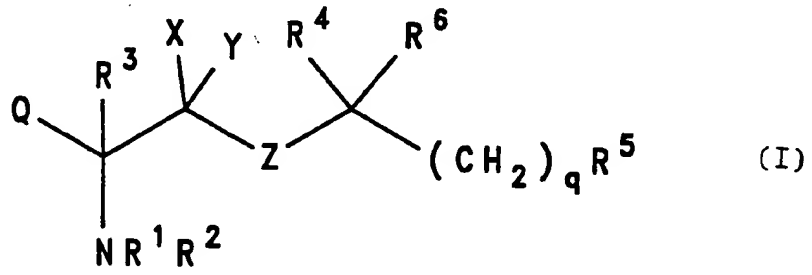
(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SUBSTITUTED AMINES AS TACHYKININ RECEPTOR ANTAGONISTS



(I)

(57) Abstract

Compounds of formula (I), and salts and prodrugs thereof, wherein Q is optionally substituted phenyl or benzhydryl; X and Y are each H or together form a group =O; Z is O, S or NR^9, where R^9 is H or C_{1-6}alkyl; R^1 represents H or C_{1-6}alkyl; R^2 represents C_{1-6}alkyl substituted by $CONR^7(CH_2)_pR^8$ (where R^7 is H or C_{1-6}alkyl, R^8 is optionally substituted heteroaryl and p is 0, 1, 2, 3, 4, 5 or 6); R^3 represents H, C_{1-6}alkyl or C_{2-6}alkynyl; R^4 represents H, C_{1-6}alkyl or optionally substituted phenyl; R^5 represents optionally substituted phenyl; R^6 is H or C_{1-6}alkyl; and q is 0, 1, 2 or 3; are tachykinin antagonists useful in therapy.

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SUBSTITUTED AMINES AS TACHYKININ RECEPTOR ANTAGONISTS

This invention relates to a class of compounds, which are useful as tachykinin receptor antagonists.

The tachykinins are a group of naturally-occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in the peripheral nervous and circulatory systems. The structures of three known mammalian tachykinins are as follows:

Substance P:

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2

Neurokinin B:

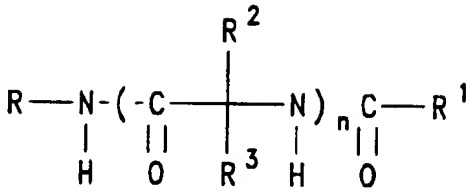
Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardivascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitus, inflammatory diseases of the gut including ulcerative colitis and Crohn disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, J. Auton. Pharmacol. (1993) 13, 23-93. Tachykinin antagonists are

also believed to be useful in allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], and immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9]. Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon et al., Cancer Research (1992) 52, 4554-7].

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophillic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosis (European patent application no. 0 436 334), conjuctivitis, vernal conjunctivitis, contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989) and emesis (European patent application no. 0 533 280).

European patent application no. 0 194 464 discloses compounds of formula (A):



(A)

wherein:

R^1 is loweralkyl, arylloweralkyl or optionally substituted phenyl;

R^2 is inter alia phenyl;

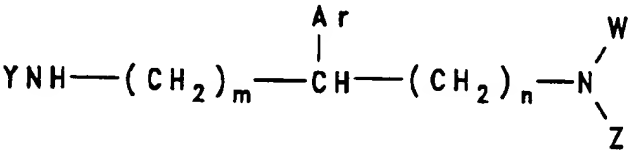
R^3 is inter alia H or loweralkyl;

R is inter alia arylloweralkyl; and

n is inter alia 1.

The compounds are said to have anticonvulsant properties.

Canadian patent application no 2,029,338 discloses compounds of formula (B):



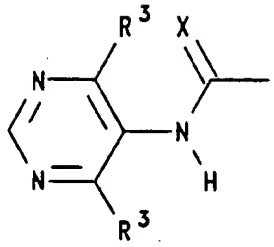
(B)

wherein

Ar is inter alia phenyl;

m is inter alia zero;

Y is H, $Ar'NHC$, $Ar'NHC$, R-C, RCH_2 or



where Ar' is optionally substituted phenyl or naphthyl, R is optionally substituted alkyl, a 5- or 6-membered heterocycle or optionally substituted phenyl, and X is O or S;

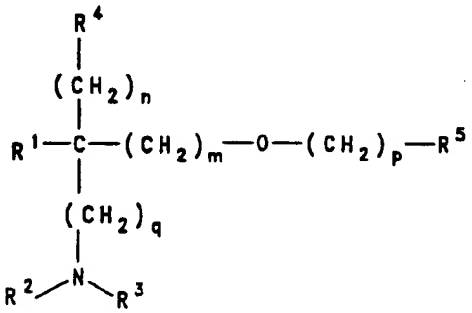
n is inter alia 1;

W is inter alia H or C_{1-20}alkyl; and

Z is inter alia R-CH_2, where R is inter alia optionally substituted phenyl.

The compounds are said to be ACAT inhibitors useful in lowering blood cholesterol levels.

British patent application no. 2054588 discloses compounds of formula (C):



(C)

wherein

R^1 is C_{1-10} alkyl;

R^2 and R^3 are H or C_{1-10}alkyl;

R^4 is inter alia optionally substituted phenyl;

R^5 is inter alia optionally substituted phenyl;

n is inter alia zero;

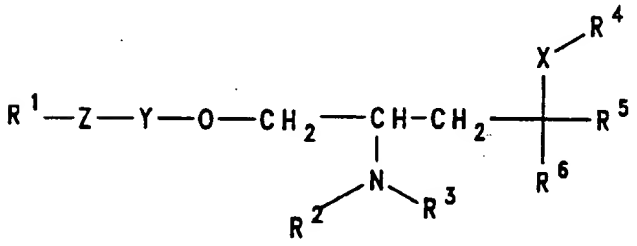
m is inter alia 1;

p is inter alia 1; and

q is inter alia zero.

The compounds are said to have anti-spasmolytic, anaesthetic and analgesic activity.

European patent appliciton no. 330 940 discloses compounds of formula (D):



(D)

wherein:

R^1 is inter alia an aromatic group;

R^2 and R^3 are C_{1-6}aliphatic, or together form a ring which may contain further heteroatoms;

R^4 is an aromatic group;

R^5 is inter alia an aromatic group;

R^6 is inter alia H;

X is a bond or CH_2;

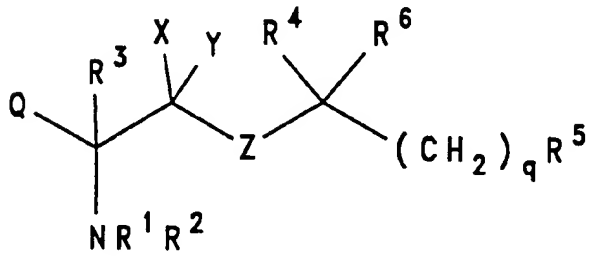
Y is inter alia C_{1-6}hydrocarbyl;

Z is inter alia a bond.

The compounds are said to have anti-depressant effect in mice.

There is no prior art disclosure of the amine substitution of the compounds of the present invention.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

Q represents optionally substituted phenyl or optionally substituted benzhydryl;

X and Y each represent H or X and Y together form a group =O;

Z represents O, S or NR^9, where R^9 represents H or C_{1-6}alkyl;

R^1 represents H or C_{1-6}alkyl;

R^2 represents C_{1-6}alkyl substituted by $CONR^7(CH_2)_pR^8$ (where R^7 is H or C_{1-6}alkyl, R^8 is optionally substituted heteroaryl and p is 0, 1, 2, 3, 4, 5 or 6);

R^3 represents H, C_{1-6}alkyl or C_{2-6}alkyenyl;

R^4 represents H, C_{1-6}alkyl or phenyl (optionally substituted by one or more of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO_2R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, $COOR^a$ or $CONR^aR^b$, where R^a and R^b each independently represent H, C_{1-6}alkyl, phenyl or trifluoromethyl);

R^5 represents phenyl optionally substituted by one or more of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo,

cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO_2R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, $COOR^a$ or $CONR^cR^b$, where R^a and R^b are as above defined;

R^6 represents H or C_{1-6}alkyl;

q is 0, 1, 2 or 3.

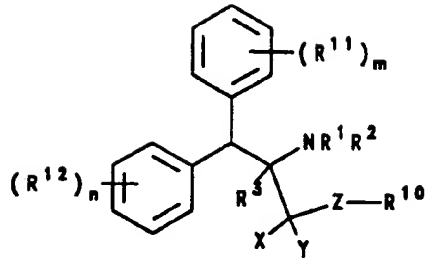
As used herein, the definition of each expression, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The alkyl, alkenyl and alkynyl groups referred to with respect to any of the above formulae may represent straight, branched or cyclic groups or combinations thereof. Thus, for example, suitable alkyl groups include methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

Where Q represents substituted phenyl or benzhydryl, suitable substituents include C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO_2R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, $COOR^a$ or $CONR^aR^b$, where R^a and R^b are as above defined. One or more substituents may be present and each may be located at any available ring position.

A subgroup of compounds of the present invention is represented by compound of formula (IA), and salts and prodrugs thereof:



(IA)

wherein R^1, R^2, R^3, X, Y and Z are as defined for formula (I);

R^{10} represents C_{1-3}alkyl substituted by a phenyl group which may itself optionally be substituted by one or more of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO_2R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, $COOR^a$ and $CONR^aR^b$, where R^a and R^b are as previously defined;

each R^{11} independently represents C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

each R^{12} independently represents C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl; and

n and m each represent 0, 1, 2 or 3.

In the compounds of formula (I) it is preferred that Q is unsubstituted phenyl or unsubstituted benzhydryl, more preferably unsubstituted benzylhydryl.

Preferably X and Y each represents H.

Suitably Z represents O or NH. Preferably Z represents O.

Suitable values for the group R^1 include H, methyl, ethyl, propyl, and cyclopropylmethyl. Preferably R^1 is H or C_{1-4}alkyl, for example methyl, ethyl or n-propyl. More preferably R^1 is H or methyl.

Suitable values for the heteroaryl moiety R^8 include thienyl, furyl, pyrrolyl, pyridyl, pyrazolyl,

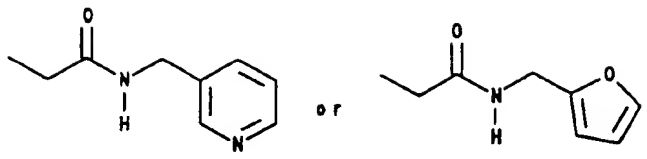
triazolyl, tetrazolyl, thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, quinolyl, isothiazolyl, imidazolyl, benzimidazolyl, benzoxazolyl, benzothiophenyl, benzofuranyl and indolyl, any of which may be substituted. Suitable substituents in the heterocyclic ring include one or more of C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, oxo, thioxo, halo, trifluoromethyl, NR^aR^b, NR^aCOR^b, $CONR^aR^b$, CO_2R^a, SR^a, SO_2R^a and CH_2OR^a where R^a and R^b are as previously defined.

Preferably the heteroaryl moiety R^8 represents a substituted or unsubstituted 5- or 6-membered aromatic heterocycle.

It will be appreciated that, when the heteroaryl moiety R^8 is substituted by an oxo or thioxo substituent, different tautomeric forms are possible so that the substituent may be represented as =O or -OH, or =S or -SH, respectively. For the avoidance of doubt, all such tautomeric forms are embraced by the present invention.

Suitable values for the C_{1-6}alkyl moiety of R^2 include CH_2, $CH(CH_3)$ and CH_2CH_2. Preferably the C_{1-6}alkyl moiety of R^2 is CH_2 or $CH(CH_3)$, more preferably $CH(CH_3)$.

Preferably R^2 represents C_{1-6}alkyl, more preferably C_{1-4}alkyl such as C_{1-2}alkyl, for example, CH_2 or $CH(CH_3)$, substituted by a group $CONR^7(CH_2)_pR^8$ where R^7 is preferably H or methyl and p is preferably 1. For example, R^2 may suitably represent:



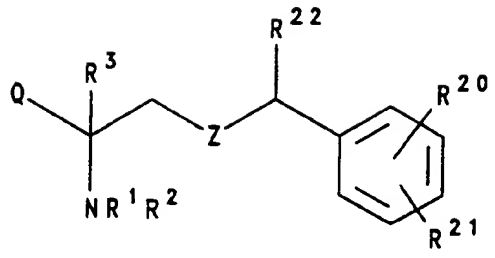
Suitable values for the group R^3 include H and methyl, preferably H.

Preferably R^4 and R^6 each independently represent H or C_{1-4}alkyl, especially methyl.

Suitably q is zero, 1 or 2, preferably zero.

Preferably R^5 represents substituted phenyl. Suitable phenyl substituents include C_{1-6}alkyl such as methyl, ethyl, i-propyl, i-butyl, t-butyl and cyclopropyl, C_{2-6}alkenyl such as vinyl, C_{1-6}alkoxy such as methoxy, ethoxy and i-propoxy, phenoxy, amino, carboxamido, carbonylmethoxy, trimethylsilyl, nitro, cyano, bromo, chloro, fluoro, iodo and trifluoromethyl. Preferably R^5 represents phenyl substituted by one or more groups selected from C_{1-4}alkyl, such as methyl and t-butyl, C_{1-4}alkoxy, such as methoxy, trifluoromethyl and halo such as bromo, chloro, fluoro and iodo. Preferably R^5 represents 3,5-disubstituted phenyl. A particularly preferred value for R^5 is 3,5-bistrifluoromethylphenyl.

A preferred sub-group of compounds according to the invention is represented by formula (IB)



(IB)

wherein Q, R^1, R^2, R^3 and Z are as defined for formula (I) above;

R^{20} represents H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO_2R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, $COOR^a$ or $CONR^aR^b$, where R^a and R^b are as above defined;

R^{21} represents C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, trifluoromethyl or OR^a;

R^{22} represents H or methyl;

and salts and prodrugs thereof.

Particularly preferred are compounds of formula (IB) wherein R^{20} is other than H and R^{20} and R^{21} are located in the 3- and 5-positions. Most preferably R^{20} and R^{21} each represent C_{1-4}alkyl, C_{1-4}alkoxy, halo or trifluoromethyl.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a

pharmaceutically acceptable non-toxic acid such as hydrochloric acid, sulphuric acid, oxalic acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Thus, for example, when R^1 is other than H, the nitrogen atom to which it is attached may be further substituted to give a quaternary ammonium salt. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The compounds according to the invention may exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The substance P antagonising activity of the compounds described herein was evaluated using the human NK1R assay described in published European patent application no. 0 528 495. The method essentially

involves determining the concentration of the test compound required to reduce by 50% the amount of radiolabelled substance P binding to human NK1R, thereby affording an IC_{50} value for the test compound. The compounds of the Examples were found to have IC_{50} values less than 100nM.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or topical administration including administration by inhalation or insufflation.

The invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), or a salt or prodrug thereof, and a pharmaceutically acceptable carrier, which process comprises bringing a compound of formula (I), or a salt or prodrug thereof into association with a pharmaceutically acceptable carrier.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is

dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are adminsitered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

For topical administration, for example as a cream, ointment or lotion, pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or arylalkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally-employed non-toxic, pharmaceutically acceptable organic and inorganic carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl

alcohol, phenyl ethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetraacetic acid, and the like.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as multiple sclerosis (MS) and amyotropic lateral sclerosis (ALS; Lou Gehrig's disease) and other neuropathological disorders such as peripheral neuropathy, for example, diabetic or chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinoma such as small cell lung cancer; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, irritable bowel syndrome, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like, and proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atropic dermatitis, urticaria, and other eczematoid dermatitis; oedema, such as oedema caused by thermal injury; addiction disorders such as

alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosis; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; emesis, including acute, delayed and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, surgery, migraine and variations in intercranial pressure; disorders of bladder function such as cystitis and bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the

treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2-adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

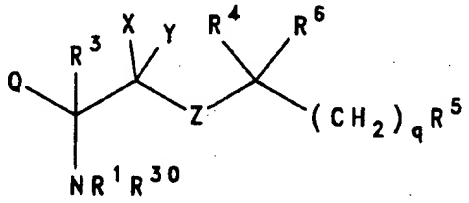
The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10

mg/kg of a compound of formula (I) per day. For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

The compounds according to the invention may be prepared by reaction of a compound of formula (II)



(II)

wherein Q, R^1, R^3, R^4, R^5, q, X, Y and Z are as defined for formula (I) and R^{30} represents C_{1-6}alkyl substituted by $COOR^{31}$, where R^{31} is H or alkyl, with an amine of formula $HNR^7(CH_2)_pR^8$, where R^7, R^8 and p are as defined for formula (I).

Where R^{31} represents H, the reaction is preferably effected in the presence of a coupling agent, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide.

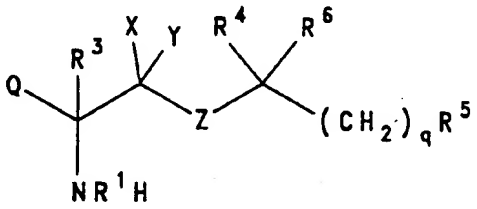
The reaction is conveniently effected in a suitable organic solvent, such a a halogenated hydrocarbon, for example, dichloromethane.

Where R^{31} represents alkyl, reaction with the amine of formula $HNR^7(CH_2)_pR^8$ is effected at elevated temperature.

Compounds of formula (II) wherein R^{31} is H may be prepared form compounds of formula (II) wherein R^{31} is alkyl, by saponification.

The saponification is conveniently effected using an alkali metal hydroxide, such as, for example, lithium hydroxide.

Compounds of formula (II) wherein R^{31} is alkyl may be prepared from compounds of formula (III)



(III)

wherein R^1, R^3, R^4, R^5, R^6, q, X, Y and Z are as defined for formula (I), by reaction with a compound of formula Hal-C_{1-6}alkyl-$COOR^{31}$, wherein Hal represents halo, such as chloro, bromo or iodo, and R^{31} represents alkyl, in the presence of a base.

Suitable bases of use in the reaction include alkali metal carbonates such as, for example, potassium carbonate.

Compounds of formula (III) may be prepared as described in published international patent applications nos. WO 93/01160 and WO 93/01165.

Compounds of formula (I) may also be prepared from other compounds of formula (I). Thus, for example, compounds of formula (I) wherein R^1 represents H may be reacted with an alkylating agent to produce compounds of formula (I) wherein R^1 represents an alkyl group. Suitable procedures are described in the accompanying

examples, or will be readily apparent to one skilled in the art.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, for example, leucine methyl esters, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

EXAMPLE 1

1-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-3,3-dipheny l-2-((N-(3-pyridylmethyl)carboxamido)methylammonium) propane bis oxalate salt

a) To a solution of diphenylmethyleneiminoacetonitrile (44g, 0.20 Mol), benzyltrimethyl ammonium chloride (4.4g, 0.024Mol) and sodium hydroxide (48.4g, 1.21Mol) in toluene (40ml) and water (90ml) was added bromodiphenylmethane (149.4g, 0.60Mol) at 0°C. After the solution had been stirred at room temperature for 5h a mixture of water (200ml), ethyl acetate (40ml) and hexane (160ml) was added. The solution was filtered and the residue washed with ethyl acetate/hexane and dried in vacuo to give 3,3-diphenyl-2-(diphenylmethyleneimino)proprionitrile 47.6g. ^{1}H NMR (360MHz, $CDCl_3$) δ 7.5-6.87 (20H, m, aryl), 4.8 (1H, d, J = 8.85H), 4.69 (1H, d, J = 9.2Hz). An analytical sample was recrystallised from ethyl acetate/hexane mp = 152-153°C.

b) 3,3-Diphenyl-2-(Diphenylmethyleneimino)proprionitrile (Example 1a, 46.7g, 0.12Mol) was heated in a solution of 5.5M-hydrochloric acid (200ml) at reflux for 48h. The solid which crystallized from the cooled solution was removed by filtration, washed with diethyl ether and dried to give $,$-diphenylalanine hydrochloride 21g. ^{1}H NMR (250MHz, DMSO d_6) δ 8.6 (3H, vbs), 7.6-7.1 (10H, m), 4.8 (1H, d, J = 10.4Hz), 4.4 (1H, d, J = 10.4Hz).

c) To a solution of 1M-lithium aluminium hydride in diethyl ether (40ml, 0.04Mol) was added $,$-diphenylalanine hydrochloride (3.70g, 0.0133Mol, Example 1b) over a period of 1h. The solution was heated at reflux for 1h, cooled to room temperature and to the solution was cautiously added 2M-sodium hydroxide (40ml). After filtering the solution through Celite, the residue was washed with ethyl acetate and the organic phase of the combined filtrates was washed with water, saturate brine and dried ($MgSO_4$). The solid which formed on removal of the solvent in vacuo was washed with hexane to give 2-amino-3,3-diphenylpropan-1-ol 2.52g, mp 107-8°C. ^1H NMR (360MHz, $CDCl_3$) δ 7.36-7.14 (10H, m), 3.79 (1H, d, J = 10.5Hz), 3.6 (1H, m), 3.57 (1H, dd, J = 10.7Hz and 3.3Hz), 3.31 (1H, dd, J = 10.7Hz and 6.7Hz), m/z (CI^+) 228 (M+H).

d) A solution of 2-amino-3,3-diphenylpropan-1-ol (2.3g, 0.010Mol, Example 1c) and di-t-butyldicarbonate (2.65g, 0.0122Mol) in dichloromethane (25ml) was stirred at room temperature for 1h. The solid which formed on removal of the solvent was recrystallized from diethyl ether to give 2-t-butoxycarbonylamino-3,3-diphenylpropan-1-ol (2.85g, mp 95-96°C. ^1H NMR (250MHz, $CDCl_3$) δ 7.34-7.15 (10H, m), 4.58 (1H, bd), 4.48 (1H, m), 4.1 (1H, d, J = 10.6Hz), 3.67 (1H, dd, J = 11.13Hz and 3.11Hz), 3.5 (1H, dd, J = 11.3Hz and 4.45Hz), 1.31 (9H, s).

e) To a solution of the product of Example 1d (8.20g) and 3,5 bis(trifluoromethyl)benzyl bromide (6.20ml) in N,N-dimethyl formamide (50ml) was added sodium hydride (80% suspension in oil, 0.90g). After stirring the solution for 2 hours, ethyl acetate

(250ml) and water (250ml) were added, the organic phase washed further with water (10 x 100ml), saturated brine (100ml) and dried ($MgSO_4$) After evaporation the residue was purified by column chromatography on silica gel (eluted with 20-75% ethyl acetate in petroleum ether) to give 1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-2-(N-t-butoxy carbonylamino)-3,3-diphenylpropane.

f) To the product of Example 1e (42g), was added a saturated solution of hydrogen chloride in diethyl ether (500ml), and the resulting solution allowed to stand at room temperature for 48hr. The precipitated hydrochloride salt was collected by filtration, washed with diethyl ether (100ml), and dried in vacuo to give 2-ammonium-1-(3,5-bis(trifluoromethyl)phenyl) methyloxy)-3,3-diphenylpropane hydrochloride salt, mp = 210°C (del.); ^1H NMR (DMSO d_6, 360MHz) δ 3.42 (1H, dd, J=4.7, 10.5Hz), 3.65 (1H, dd, J=2.6, 10.5Hz), 4.24 (1H, d, J=11.9Hz), 4.50 (1H, m), 4.53 (1H, d, J=13Hz), 4.67 (1H, d, J=13Hz), 7.18 (1H, m), 7.26 (3H, t, J=7.7Hz), 7.36 (4H, m), 7.53 (2H, d, J-7.4Hz), 8.03 (1H, s), 8.05 (2H, s), 8.08 (2H, bs).

g) 2-Amino-1-(3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylpropane (0.365g, Example 1f, liberated from its hydrochloride salt by partitioning between ethyl acetate and 10% aqueous sodium carbonate solution followed by drying ($MgSO_4$) and evaporation in vacuo), K_2CO_3 (0.5g), and methyl bromacetate (1.23g) were stirred in dimethyl formamide (5ml) for 30 minutes. Ethyl acetate (50ml) and water (50ml) were added and the organic phase was washed further with water (50ml), saturated brine (50ml) and dried ($MgSO_4$). After evaporation the residue was chromatographed on silica gel (eluting with

ethyl acetate: hexane (4:6)) to give 1-(3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenyl-2-(N-((carbomethoxy)methyl)amino)propane as an oil.

h) To a solution of 1-((3,5-bis (trifluoromethyl)phenyl)methyloxy)-2-(N-((carbomethoxy) methyl)amino)-3,3-diphenylpropane (Example 1g, 2.38g) in tetrahydrofuran (25ml) was added 1M-potassium hydroxide solution (25ml) and the mixture heated to reflux for 16 hours. The solvent was removed by evaporation and 1M-hydrochloric acid was added to an aqueous solution of the residue until pH = 2. The gum which formed was recrystallised from aqueous ethanol to give N-(1-((3,5-bis(trifluoromethyl) phenyl)methyloxy)-3,3- diphenylprop-2-yl)glycine mp 116-119°C; m/e (CI^+) 512 (M+H), (CI^-) 511 (M). Found: C, 60.06; H, 4.55; N, 2.66; $C_{26}H_{23}NO_3F_6.0.5(H_2O)$ requires C, 60.00; H, 4.64; N, 2.69%.

i) To a solution of the product of Example 1h (0.350g), 3-aminomethylpyridine (70ml), 1-hydroxybenzotriazole (0.092g) and triethylamine (0.190ml) in dichloromethane (10ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.131g). After stirring the solution for 16 hours water was added and the organic phase dried ($MgSO_4$). After evaporation in vacuo and column chromatography on silica gel (eluting with 20% to 100% ethyl acetate in petroleum ether) to give 1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenyl-2-((N-(3-pyridylmethyl)carboxamido)methylammonium)propane bis oxalate salt, m/e (CI^+)=602 (M+H), (CI^-)=600 (M-H). Found: C, 54.54; H, 4.39; N, 5.20; $C_{32}H_{29}N_3O_2F_6.2 \times C_2H_2O_4. 0.5 \times H_2O$ requires C, 54.68; H, 4.33; N, 5.31%.

EXAMPLE 2

1-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenyl-2-((N-(2- furfurylmethyl)carboxamido) methylammonium)propane oxalate salt

The title compound was prepared from N-(1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl)glycine (Example 1h) using an analgous coupling procedure as described in Example 1i. m/e FAB$^+$ 91. Found: C, 57.49; H, 4.53; N, 4.19; $C_1H_{28}N_2O_3F_6$. ($C_2H_2O_4$). 0.5 x (H_2O) requires C, 57,47; H, 4.53; N, 4.06%.

EXAMPLE 3

1-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenyl-2-((N-(2-pyridylmethyl)carboxamido)methylammonium)propane oxalate salt

The title compound was prepared from N-(1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenylprop-2-yl) glycine (Example 1h) using an analogous coupling procedure as described in Example 1i, mp = 124-126°C; m/e FAB$^+$ 602. Found: C, 55.85; H, 4.40; N, 5.75; $C_{32}H_{29}N_3O_2F_6$. 1.75 x ($C_2H_2O_4$) requires C, 56.16; H, 4.31; N, 5.53%.

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 4A Tablets containing 1-25mg of compound

	Amount mg		
Compound of formula (I)	1.0	2.0	25.0
Microcrystalline cellulose	20.0	20.0	20.0
Modified food corn starch	20.0	20.0	20.0
Lactose	58.5	57.5	34.5
Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 4B Tablets containing 26-100mg of compound

	Amount mg		
Compound of formula (I)	26.0	50.0	100.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	213.5	189.5	139.5
Magnesium Stearate	0.5	0.5	0.5

The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

EXAMPLE 5 Parenteral injection

	Amount mg
Compound of formula (I)	1 to 100mg
Citric Acid Monohydrate	0.75mg
Sodium Phosphate	4.5mg
Sodium Chloride	9mg
Water for Injections	to 1ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

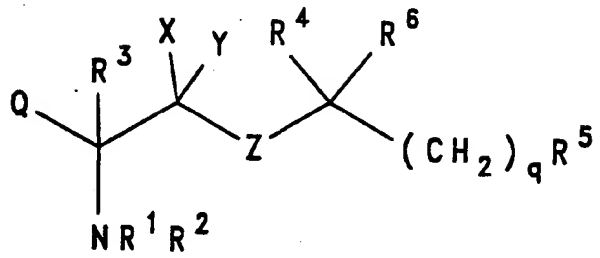
EXAMPLE 6 Topical formulation

	Amount mg
Compound of formula (I)	1-10g
Emulsifying Wax	30g
Liquid paraffin	20g
White Soft Paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

CLAIMS:

1. A compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

Q represents optionally substituted phenyl or optionally substituted benzhydryl;

X and Y each represent H or X and Y together form a group =O;

Z represents O, S or NR^9, where R^9 represents H or C_{1-6}alkyl;

R^1 represents H or C_{1-6}alkyl;

R^2 represents C_{1-6}alkyl substituted by $CONR^7(CH_2)_pR^8$ (where R^7 is H or C_{1-6}alkyl, R^8 is optionally substituted heteroaryl and p is 0, 1, 2, 3, 4, 5 or 6);

R^3 represents H, C_{1-6}alkyl or C_{2-6}alkyenyl;

R^4 represents H, C_{1-6}alkyl or phenyl (optionally substituted by one or more of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO_2R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, $COOR^a$ or $CONR^aR^b$, where R^a and

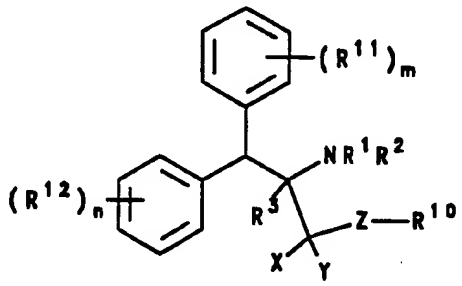
R^b each independently represent H, C_{1-6}alkyl, phenyl or trifluoromethyl);

R^5 represents phenyl optionally substituted by one or more of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO_2R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, $COOR^a$ or $CONR^cR^b$, where R^a and R^b are as above defined;

R^6 represents H or C_{1-6}alkyl;

q is 0, 1, 2 or 3.

2. A compound as claimed in claim 1 of formula (IA), or a salt or prodrug thereof:



(IA)

wherein R^1, R^2, R^3, X, Y and Z are as defined for formula (I);

R^{10} represents C_{1-3}alkyl substituted by a phenyl group which may itself optionally be substituted by one or more of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^a, SOR^a, SO_2R^a, OR^a, NR^aR^b, NR^aCOR^b, NR^aCOOR^b, $COOR^a$ and $CONR^aR^b$, where R^a and R^b are as previously defined;

each R^{11} independently represents C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl;

each R^{12} independently represents C_{1-6}alkyl, C_{1-6}alkoxy, halo or trifluoromethyl; and

n and m each represent 0, 1, 2 or 3.

3. A compound as claimed in claim 1 wherein Q represents optionally substituted benzhydryl.

4. A compound as claimed in claim 1 or claim 3 wherein R^5 represents phenyl substituted by one or more groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl and halo.

5. A compound as claimed in claim 1, claim 3 or claim 4 wherein R^4 and R^6 each independently represent H or C_{1-4}alkyl.

6. A compound as claimed in any preceding claim wherein p is 1 and R^8 is selected from thienyl, furyl, pyrrolyl, pyridyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, oxazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, quinolyl, isothiazolyl, imidazolyl, benzimidazolyl, benzoxazolyl, benzothiophenyl, benzofuranyl and indolyl, any of which may be substituted.

7. A compound as claimed in any preceding claim wherein X and Y each represent H and Z represents O.

8. A compound as claimed in claim 1 selected from:

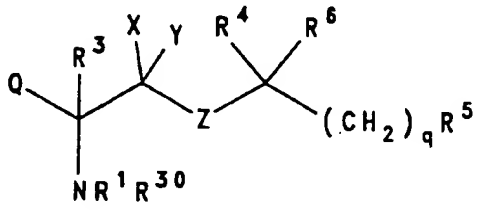
1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenyl-2-((N-(3-pyridylmethyl)carboxamido) methylammonium propane;

1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenyl-2-((N-(2-furfurylmethyl)carboxamido) methylammonium propane;
1-((3,5-bis(trifluoromethyl)phenyl)methyloxy)-3,3-diphenyl-2-((N-(2-pyridylmethyl)carboxamido) methylammonium propane;
and salts and prodrugs thereof.

9. A compound as claimed in any preceding claim for use in therapy.

10. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 8 in association with a pharmaceutically acceptable carrier.

11. A process for the preparation of a compound as claimed in claim 1, which process comprises reacting a compound of formula (II):



(II)

wherein Q, R^1, R^3, R^4, R^5, R^6, q, X, Y and Z are as defined for formula (I), and R^{30} represents C_{1-6}alkyl substituted by $COOR^{31}$, where R^{31} is H or alkyl, with an amine of formula $HNR^7(CH_2)_pR^8$.

12. A method for the treatment or prevention of a physiological disorder associated with an excess of

tachykinins, which method comprises administration to a patient in need thereof of a tachykinin-reducing amount of a compound according to claim 1.

13. A method according to claim 12 for the treatment or prevention of pain or inflammation.

14. A method according to claim 12 for the treatment or prevention of migraine.

15. A method according to claim 12 for the treatment or prevention of arthritis.

16. The use of a compound as claimed in any one of claims 1 to 8 for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins.

17. The use of a compound as claimed in any one of claims 1 to 8 for the manufacture of a medicament for the treatment of pain or inflammation.

18. A process for preparing a composition as claimed in claim 10 which process comprises bringing a compound as claimed in any of claims 1 to 8 into association with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/GB 93/01601

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D213/40 A61K31/44 C07D307/52 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 194 464 (RESEARCH CORPORATION) 17 September 1986 cited in the application ---	
A	EP,A,0 432 442 (WARNER LAMBERT CO) 19 June 1991 & CA,A,2 029 338 cited in the application ---	
A	GB,A,2 054 588 (SOCIETE INDUSTRIELLE DE PRODUITS DE SYNTHESE) 18 February 1981 cited in the application ---	
A	EP,A,0 330 940 (BOEHRINGER MANNHEIM) 6 September 1989 cited in the application --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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Date of the actual completion of the international search	Date of mailing of the international search report
3 November 1993	15. 11. 93

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